# Canine Cushing's Syndrome: medical treatment

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**Canine Cushing's Syndrome: medical treatment**

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Although hypercortisolism (HC) is not a life-threatening disease, it can lead to serious complications (e.g. diabetes mellitus, hypertension, pyelonephritis, pulmonary thromboembolism) and have a considerable impact on the animal's quality of life. Elimination of clinical signs of glucocorticoid excess is the main goal of treatment. Depending on the form of HC, this can be achieved by hypophysectomy, adrenalectomy, or medical therapy. The following report is restricted to the medical treatment of HC.

**Mitotane**

For a long time, mitotane was the drug of choice in treating HC. Mitotane selectively destroys the adrenal cortex, either partially or completely, depending on the treatment protocol used. The efficacy of mitotane is favorable, and > 80% of dogs with pituitary-dependent HC show a good to excellent response.[1] Mitotane has several disadvantages, which include the potential development of adrenocortical insufficiency, possible drug intolerances, and a high frequency of relapses during treatment.[1] As the side effects of mitotane therapy can be severe and the relapses frustrating, most veterinarians nowadays use trilostane as the first-line treatment for HC.

**Trilostane**

In 1998, trilostane was described for the first time in veterinary medicine as a treatment for dogs with HC.[2] Since then, the drug has gained wide popularity and is now licensed for use in dogs with pituitary-dependent HC under the name Vetoryl. Trilostane is a competitive inhibitor of the 3β-hydroxysteroid dehydrogenase/$\Delta^{5,4}$-isomerase enzyme system (3β-HSD).[3] The 3β-HSD is essential for the biosynthesis of all classes of steroid hormones, namely glucocorticoids, mineralocorticoids, progesterone, androgens and estrogens (Figure 1). Trilostane blocks the conversion of pregnenolone to progesterone and therefore the production of its end-products cortisol, aldosterone and androstenedione.

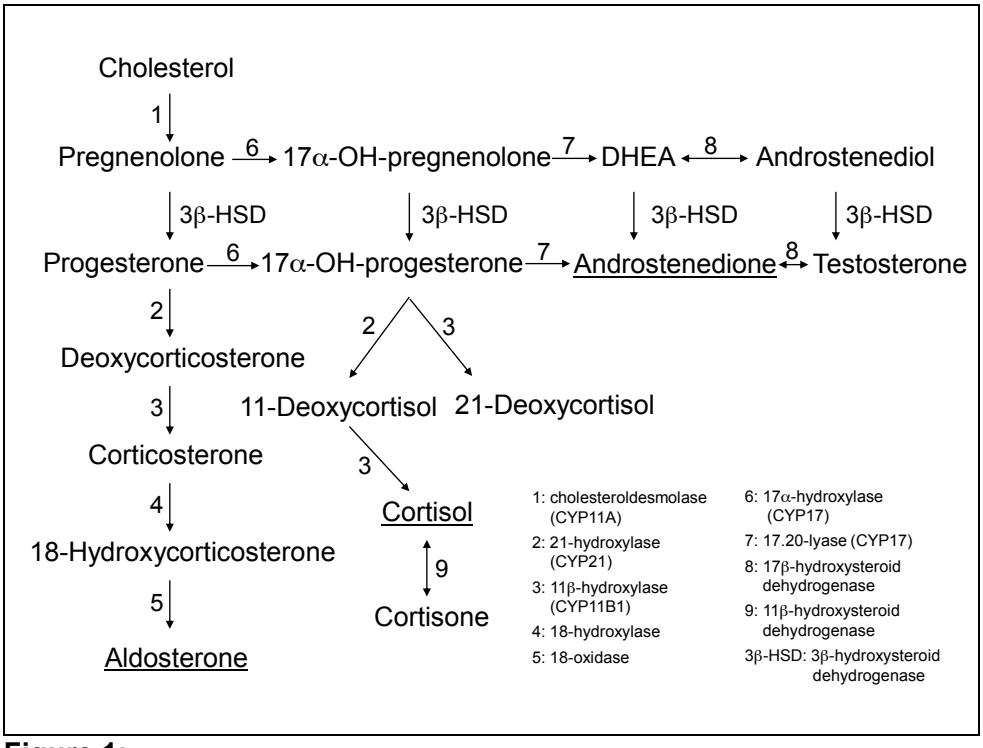


**Figure 1:**
Illustration of the biosynthetic pathway and enzymes for mineralocorticoids, corticoids, and androgens in the adrenal cortex.

Studies in dogs confirmed that trilostane inhibits the 3β-HSD in this species.[4] However, additional effects more distal in the enzyme cascade, possibly on the 11β-hydroxylase and on the interconversion of cortisol and cortisone by the 11β-hydroxysteroid dehydrogenase are also discussed.[4,5] Furthermore, an effect of trilostane on the intracellular glucocorticoid receptor, as in rats, also seems possible in dogs.[6]
Trilostane has low water solubility and is best absorbed with food. Furthermore, in the liver, trilostane has to be converted into active metabolites (e.g. ketotrilostane). Differences in absorption, metabolism or in its inhibiting effects on different enzymes within the adrenal glands may be reasons for variability in plasma levels and unequal activity between individuals.
It is well known that the effect of trilostane does not last for 24 hours. Peak plasma levels of trilostane and ketotrilostane occur 1.5-2 hours after ingestion, and concentrations return to baseline after about 10-18 hours.[7] Consequently, results of the ACTH stimulation test depend on the interval between drug administration and testing. In a recent study post-ACTH cortisol levels were significantly higher when the ACTH stimulation test was started 4 hours after trilostane administration compared to 2 hours after administration.[8]

*Starting dose and frequency*
When trilostane was introduced onto the veterinary market the recommended starting dose was 2-10 mg/kg once daily. Nowadays however, frequent users agree on much lower doses. We recommend a starting dose of 1-2 mg/kg once daily or 0.5-1 mg/kg twice daily. Larger dogs (> 15 kg) need lower doses and should therefore be started on 1 mg/kg once daily or 0.5 mg/kg twice daily.[9]
Several studies suggest using trilostane twice daily instead of once daily. Twice daily administration seems to lead to a slightly faster control of the disease and possibly increases the number of dogs with good clinical control.[10,11] However, the consequence of twice daily therapy for owner compliance also has to be considered. The decision on whether to give trilostane once or twice daily should probably be made together with the owner. Dogs with concurrent diseases influenced by high cortisol levels (e.g. diabetes mellitus) as well as cats, should be started on 0.5-1 mg/kg twice daily.
Trilostane absorption is increased by food. Therefore, owners should be told to administer trilostane with food.

*Timing of dose adjustments*
Regardless of the starting dose, dose adjustments, either up or down, will be required during the course of treatment.[12-14] The first recheck should be planned after approximately 10-14 days. At that time, however, the dose should only be changed if either the post-ACTH cortisol concentration is less than ideal (see below) or if no clinical improvement has been noted and the post-ACTH cortisol concentration is still much higher than ideal. Cortisol concentrations decrease up to 4 weeks after treatment start, even if the dog remains on the same dose. Further rechecks are recommended after about 4, 8, 12 and 16 weeks and thereafter every 3-6 months. In general, many dogs need initial dose increases and later, during long-term therapy, dose decreases. Adjustments of trilostane doses should be made in increments of 2.5-5 mg/dog/day depending on the dog's size.

*Timing of monitoring*
At the moment trilostane treatment is monitored by regular ACTH-stimulation tests. Clinical signs reported by the owners are used in addition to the post-ACTH cortisol to guide therapy. The timing of post-pill sampling is most important. It is well known that post-ACTH cortisol varies depending on the interval between dosing and testing. Therefore, it is important to keep the interval constant for each patient from test to test. We perform the ACTH stimulation test 2-3 hours post-pill and use a reference range of 2-5 ug/dl (55-135 nmol/l) for the post-ACTH cortisol. The same treatment goals are used for dogs on both once- and twice-daily therapy.
Synthetic ACTH has become expensive and at times availability has even been a problem. Additionally, a discrepancy between results of the ACTH stimulation test and clinical signs is

sometimes observed, calling into question the reliability of the ACTH stimulation test as a monitoring method. Therefore, alternatives for treatment monitoring are warranted. Clinical signs reported by owners are highly subjective and do not seem reliable as the sole monitoring method. Several studies evaluated baseline cortisol values multiple hours after trilostane administration to monitor treatment.[15,16,17] Although the studies are difficult to compare, it was shown that baseline cortisol concentrations show considerable overlap between dogs with excessive, adequate or inadequate control of cortisol release. Low baseline cortisol concentrations were not a reliable indication for excessive control.[16,17] Therefore the authors concluded that the baseline cortisol concentration should not be used as the sole monitoring tool in guiding trilostane therapy.[16,17] In two recent studies, the pre-trilostane cortisol levels (cortisol concentrations just before the next trilostane dose), the 3-hour post trilostane cortisol level or a combination of the two seem very promising as future monitoring methods for trilostane therapy.[18,19] Further studies are needed to evaluate these new cortisol monitoring methods in a larger population of dogs.

*Efficacy*

In the majority of patients trilostane is highly effective in suppressing cortisol secretion and controlling clinical signs. Many clinical signs (e.g. decreased activity, polyuria and polydipsia) resolve quickly, but certain ones (e.g. dermatological abnormalities, pendulous abdomen) can take several months to improve.[12-14] A small proportion of dogs with HC are not well controlled with trilostane.

In dogs with concurrent diabetes mellitus, insulin requirements and fructosamine concentrations do not consistently decrease during trilostane treatment.[20] Prospective reduction in insulin doses at the start of trilostane treatment is probably not warranted.[20]

Trilostane does work in adrenal-dependent HC. Still, however, adrenalectomy remains the treatment of choice for this form of HC. If surgery is not an option either mitotane or trilostane can be used. Comparison of the median survival times between mitotane and trilostane treated dogs with adrenal-dependent HC revealed no significant difference.[21,22] The only factor which significantly affected survival was the presence of metastases.[21] Although these studies have limitations and the numbers of dogs included were small, it seems that the use of mitotane in adrenal-dependent HC does not confer a major clinical advantage.

*Safety*

Adverse effects of trilostane are seen in 10-25% of cases and are usually mild and self-limiting (e.g. gastrointestinal signs).[12-14] However, trilostane not only lowers cortisol concentrations but also (to a lesser extent) aldosterone concentrations.[23] Excess adrenal gland suppression can therefore occur and warrants immediate discontinuation of trilostane therapy. As trilostane is a competitive enzyme inhibitor, its effect should be rapidly reversible. However, in some cases adrenal suppression can last weeks to years. In these cases adrenal necrosis may be suspected, possibly induced by the elevated ACTH concentrations during therapy.[24,25]

When hypoadrenocorticism is suspected, we recommend discontinuing trilostane therapy and, depending on clinical signs, administering a few days of prednisolone and possibly IV fluids. We usually wait with re-introducing trilostane therapy until the clinical signs of HC return. Before re-starting trilostane therapy, we prefer to perform an ACTH stimulation test to document adrenal restoration. Trilostane should then be re-introduced at a very low dose (0.1-0.5 mg/kg) and increased very slowly.

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